ASPIRIN

by H. O. J. COLLIER

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ASPIRIN

The most widely consumed drug owes its dramatic effectiveness in reducing pain and fever to a broader function: moderating the varied defensive responses evoked in the body by disease

by H. O. J. Collier

The most widely used drug in the world—if we accept one medical dictionary's definition of a drug as "any substance employed as a medicine in the treatment of disease" and consider disease to imply all the minor aches, pains and chills that flesh is heir to—is aspirin. Even if we expand the definition of a drug to include the active principles of alcoholic drinks, coffee, tea and tobacco, aspirin would follow grain alcohol, caffeine, nicotine and possibly other substances consumed as chemical comforts rather than medicaments in the number of effective doses taken. In 1962 the production of aspirin in the U.S. alone was 27.2 million pounds. The consumption of aspirin tablets was 15 billion, plus a somewhat larger number containing aspirin mixed with caffeine, codeine or other substances. In spite of this massive acceptance of aspirin as an analgesic, or mitigator of pain, its exact mode of action within the body remains obscure. Evidently it works not hy blocking some agent of disease but by moderating such aspects of the body's defensive response as fever, pain and inflammation.

CHEMICAL ANCESTRY of acetylsalicylic acid, the chemical now known as aspirin, is traced on opposite page to plants in which salicylates were found. Formulas for the chemical relatives of salicylic acid are given below, with techniques used in isolating it, the chemists who performed the steps and physicians who reported medical uses of the drug. A method of acetylating salicylic acid to weaken its acidity was devised as early as 1853, but only in the last decade of the century was the process refined to make possible large-scale manufacture. The salts of aspirin (*bottom*) are more soluble, are more quickly absorbed into the bloodstream and are less injurious to the digestive tract.

The chemical component of aspirin is acetylsalicylic acid; this compound and its various salts appear under 56 proprietary names in the current *Pharmacological and Chemical Synonyms.* One of these is "Aspirin," the name under which the compound was introduced for medicinal purposes by the German firm of Bayer in 1899. Since that time wars and widespread usage have negated the effect of trade-mark laws in some countries and have deprived the name of its proprietary exclusiveness. In Germany, however, "Aspirin" remains the valuable trade-mark of the original manufacturer.

The name itself, a roundabout contraction of acetylsalicylic acid, represents one of the first exercises in the peculiar art of applied etymology that the merchandising specialists of the pharmaceutical industry have brought to such a high point of elaboration today. The prefix "a-" stands for the acetyl group that Charles Frédéric Gerhardt of Strasbourg first added to salicylic acid in 1853. The root, "spir," stands for *spirsäure,* the name given hy Karl Jakob Löwig of Cermany to the acid he prepared in 1835 from an aldehyde that Johann S. F. Pagenstecher, a Swiss pharmacist, had distilled several years earlier from the flowers of the meadowsweet (*Spiraea ulmaria*). Löwig's *spirsäure* is salicylic acid, a substance occurring in the form of esters in several plants. The diversity of natural sources of the acid resulted in more than one line of descent in the pharmacopoeia [*see illustration on opposite page*].

On June 2, 1763, a paper entitled "An Account of the Success of the Bark of the Willow in the Cure of Agues" was read to the Royal Society of London. The authorship of this first description of the effects of salicylic acid was recorded inaccurately. At the head of the paper, as printed in the *Philosophical Transactions of the Royal Society of London,* the author is named Edmund Stone; at the foot he has become Edward Stone [*see illustration on next page*]. The original manuscript bears the abbreviated signature of either "Edw^{d}" or "Edm^{d}." An Edmund Stone was elected to the Royal Society in 1725 and was still a fellow in 1763, but he was a mathematician. A protégé of the Duke of Argyll, on whose estate he had been a gardener, Edmund's gifts came to light accidentally when the duke found that his gardener possessed a copy of Newton's *Principia* and was conversant with its contents. It is probable, however, that the author of the "Account of the Success of the Bark of the Willow" was one Edward Stone, a clergyman of Chipping Norton in Oxfordshire. The printer of the *Philosophical Transactions* apparently confused him with the better-known Edmund.

Edward Stone recommended a decoction of the bark of the white willow for treating "aguish and intermitting disorders," a description of malaria. Two coincidences bolstered Stone's proposal to try willow bark against malaria. First, the bark tasted extraordinarily bitter, as does cinchona, the Peruvian bark that was then acknowledged to be the sovercign remedy for malaria. Second, the willow grows in damp and marshy places, which in Stone's day were often malarial and where, in accordance with the contemporary medical "doctrine of signatures," he would have expected to find a cure for the disease.

Stone's decoction did indeed relieve the feverish symptoms of malaria because, as chemists later learned, it contains salicylic acid, an antipyretic com-

BARK OF WILLOW
(SALIX)
(EFFECT ON MALARIA; 1763, STONE)

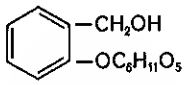
MEADOWSWEET FLOWER
(SPIRAEA)

OIL OF WINTERGREEN
(GAULTHERIA)

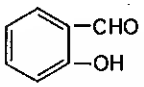
EXTRACTION;
1826–1829, BRUGNATELLI, FONTANA; LEROUX

DISTILLATION;
1831, PAGENSTECHER

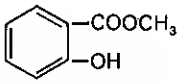
EXTRACTION;
1843, PROCTER; CAHOURS



SALICIN
(EFFECT ON RHEUMATIC FEVER;
1874–1876, MACLAGAN)



SALICYLALDEHYDE



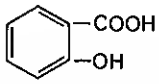
METHYL SALICYLATE

HYDROLYSIS AND OXIDATION;
1838, PIRIA

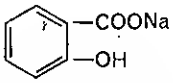
OXIDATION;
1835, LOWIG

HYDROLYSIS;
1843, CAHOURS

SYNTHESIS;
1852, GERLAND;
1860, KOLBE, LAUTEMANN

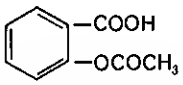


SALICYLIC ACID ("SPIRSÄURE")
(EFFECT ON RHEUMATIC FEVER;
1876, RIESS, STRICKER)

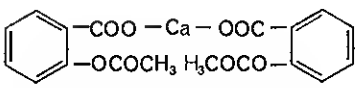


SODIUM SALICYLATE
(EFFECT ON GOUT, ARTHRITIS,
NEURALGIA; 1877, SEE)

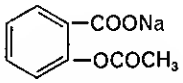
ACETYLATION;
1853, GERHARDT; 1893, HOFMANN



ACETYLSALICYLIC ACID (ASPIRIN)
(EFFECT ON RHEUMATIC FEVER
1899, WITTHAUER, WOHLGEMUT
ON PAIN; 1900, WITTHAUER)



CALCIUM ACETYLSALICYLATE



SODIUM ACETYLSALICYLATE

pound. It did not cure the disease, however, because willow bark does not contain quinine, the ingredient in cinchona bark that acts directly against the malarial parasite. Stone's recommendation of willow bark unfortunately led to the adulteration of cinchona bark with a less curative (and less expensive) material.

In 1829 a French pharmacist named H. Leroux isolated from a willow-bark extract salicin, a compound of glucose and salicyl alcohol. Salicylic acid itself was derived from this compound in 1838 by Raffaele Piria of Naples three years after Löwig had extracted the same acid from meadowsweet flowers. In 1842 William Procter of the U.S. and Auguste Cahours of France obtained methyl salicylate from oil of wintergreen; Cahours later carried the isolation a step further to salicylic acid. Since then the chemical relatives of salicylic acid have turned up in many plants. A salicylate has also been found in the secretion of the beaver's prepuce that is known as castoreum; the substance is perhaps derived from the bark of trees on which beavers subsist.

The purification and identification of salicylates occurring in nature facilitated their synthesis in the laboratory. In 1852 H. Gerland synthesized salicylic acid, and by the end of the decade Hermann Kolbe and E. Lautemann had developed a practical method of preparing it in sufficient quantity for therapeutic use. As chemists had been encouraged to synthesize salicylates by reports of medical interest, physicians were now aided in their research by the availability of salicylic acid and its purified esters.

In 1874, more than a century after Edward Stone's communication to the Royal Society, a Scottish physician named T. J. MacLagan echoed Stone's original proposal. He wrote: "Nature seeming to produce the remedy under climatic conditions similar to those which give rise to the disease... among the Salicaceae... I determined to search for a remedy for acute rheumatism. The bark of many species of willow contains a bitter principle called salicin. This principle was exactly what I wanted."

MacLagan did not, however, have to make his own decoction from the willow bark. With salicin available in pure form, he proceeded to a historic experiment: "I had at the time under my care a well-marked case of the disease which was being treated by alkalies but was not improving. I determined to give him salicin; but before doing so, took myself first five, then ten, and then thirty grains without experiencing the least inconvenience or discomfort. Satisfied as to the safety of its administration, I gave to the patient referred to twelve grains every three hours. The results exceeded my most sanguine expectations."

History was repeating itself, not only in the invocation of the doctrine of signatures that gave rise to the discovery but also in the way the remedy worked, because salicin and its derivatives no more destroy the infecting bacteria that initiate the immunological process culminating in rheumatic fever (as acute rheumatism is now often called) than they kill the malaria parasite that caused Stone's agues. Salicylates act by lessening the fever and painful inflammation that form part of the body's immunological response to some substance produced by the infecting bacteria.

MacLagan was the first physician to treat rheumatic fever successfully with salicylates, but a few months before his paper on salicin appeared in *The Lancet* of March 4, 1876, L. Riess and S. Stricker had separately reported in Berlin that

XXXII. *An Account of the Succeſs of the Bark of the Willow in the Cure of Agues. In a Letter to the Right Honourable* George *Earl of* Macclesfield, *Preſident of R. S. from the Rev. Mr.* Edmund Stone, *of* Chipping-Norton *in* Oxfordſhire.

My Lord,

Read June 2d, 1763.

AMong the many uſeful diſcoveries, which this age hath made, there are very few which, better deſerve the attention of the pnblic than what I am going to lay before your Lordſhip.

There is a bark of an Engliſh tree, which I have found by experience to be a powerful aſtringent, and very efficacious in curing aguiſh and intermitting diſorders.

About ſix years ago, I accidentally taſted it, and was ſurpriſed at its extraordinary bitterneſs; which immediately raiſed me a ſuſpicion of its having the properties of the Peruvian bark. As this tree delights in a moiſt or wet ſoil, where agues chiefly abound, the general maxim, that many natural maladies carry their cures along with them, or that their remedies lie not far from their cauſes, was ſo very appoſite to this particular caſe, that I could not help applying it;

cinnamon or lateritious colour, which I believe is the caſe with the Peruvian bark and powders.

I have no other motives for publiſhing this valuable ſpecific, than that it may have a fair and full trial in all its variety of circumſtances and ſituations, and that the world may reap the benefits accruing from it. For theſe purpoſes I have given this long and minute account of it, and which I would not have troubled your Lordſhip with, was I not fully perſuaded of the wonderful efficacy of this Cortex Salignus in agues and intermitting caſes, and did I not think, that this perſuaſion was ſufficiently ſupported by the manifold experience, which I have had of it.

I am, my Lord,

with the profoundeſt ſubmiſſion and reſpect,

Chipping-Norton, Oxfordſhire, April 25, 1763.

your Lordſhip's moſt obedient humble Servant

Edward Stone.

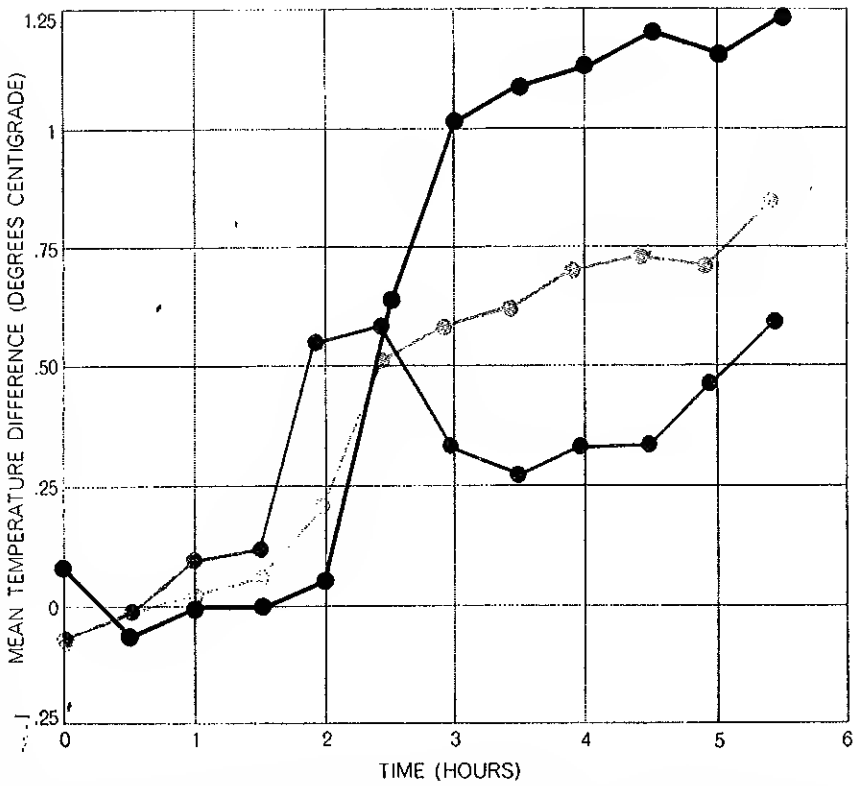
UNCERTAIN AUTHORSHIP of first paper to describe medicinal effects of willow-bark extract can be traced to a printer's error in the *Philosophical Transactions* of 1763. At top of paper (*left*) the author is named Edmnnd Stone. At bottom (*right*) the name is Edward. "Doctrine of signatures" is synopsized in the proposition that "many natural maladies carry their cures along with them...."

salicylic acid was effective in treating the disease. In the following year Germain Sée announced in Paris that salicylates also relieved chronic rheumatoid arthritis and gout. By this time several physicians had noted that salicylates detectably but not dramatically lessened certain nonrheumatic pains such as neuralgia and headache.

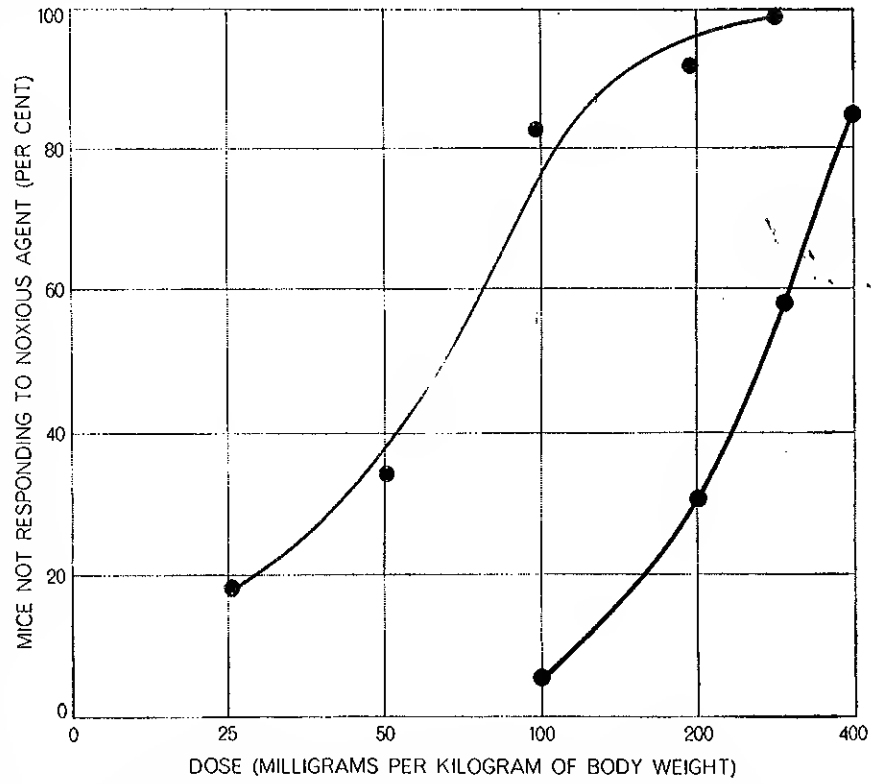
Although salicylic acid was probably the wonder drug of its day, its success was diminished by the irritation and damage it caused to the moist membranes lining the mouth, gullet and stomach. The molecule of the acid contains a hydroxyl group (OH) and a carboxyl group (COOH) extending from the six-carbon-atom benzene ring. The carboxyl group can dissociate on contact with the moist lining of the stomach wall to yield a hydrogen ion. The resulting acidity can be neutralized by replacing the hydrogen atom of the carboxyl group with an atom of a metal such as sodium. This salt, sodium salicylate, was less irritating than the acid and was prescribed by physicians, but it had to be administered in a solution that many people found to have an "obnoxious sweetish taste." Thus although the great potential of salicylic acid had been demonstrated as early as 1876, many of those to whom it was administered were distressed by its damaging effect on the lining of the digestive tract or by the unpleasant taste of the sodium salt.

Ironically the key step in successfully improving the drug's palatability had been demonstrated in 1853 by Cerhardt. He had replaced the hydrogen atom of the hydroxyl group with an acetyl group ($COCH_3$), but his method was cumbersome enough to discourage further investigation for some time. It was 40 years before Felix Hofmann, a Bayer chemist, found a simpler way to make the acetyl compound of salicylic acid. Hofmann had a personal interest in the task because his father was one of those sufferers from rheumatism who could not stomach sodium salicylate. After Hofmann's successful acetylation, his colleague Heinrich Dreser conducted an impressive exploration of the properties of acetylsalicylic acid.

"It is self-evident," he wrote, "that only a salicylate compound which is split as soon as possible in the blood with liberation of salicylic acid has medicinal value." Dreser performed several experiments on the breakdown of acetylsalicylic acid in the body, including some on himself. He swallowed a solution containing one gram of sodium acetylsalicylate, a salt in which the hydrogen

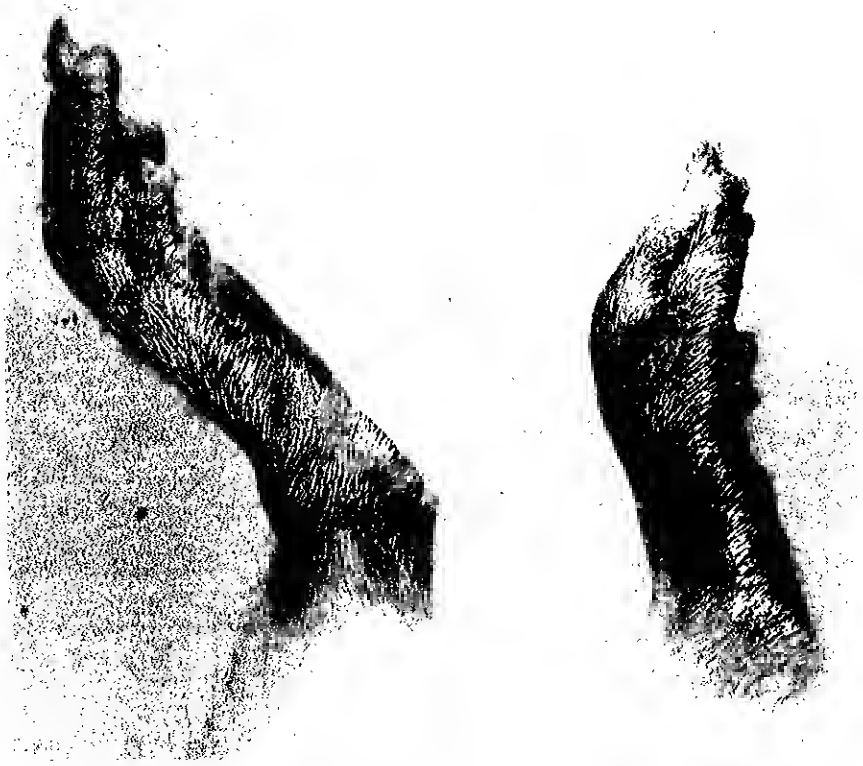


ANTIPYRETIC EFFECT of aspirin is graphed by plotting against time the rise in fever (*vertical axis*) of rabbits treated with pyrogen and aspirin. Dark-colored curve shows fever of rabbits receiving 66.7 milligrams of aspirin per kilogram of body weight. Light-colored curve depicts 22.2 milligrams per kilogram dose. Control animals (*black curve*) got no aspirin.



ANALGESIC EFFECT of aspirin (*colored curve*) is shown to exceed that of free salicylate. On horizontal axis is dosage of each drug given to mice before injection of phenylquinone, a noxious chemical. Vertical axis shows per cent that did not manifest any pain thereafter. Experiment was performed by L. C. Hendershot and J. A. Forsaith at Dow Chemical Company.

ARTHRITIC INFLAMMATION in hind feet of a rat that had received an injection of dead tubercle bacilli 13 days earlier is shown in this photograph. Precise nature of the swelling and response of arthritic rats to drugs provide a "model" of human rheumatoid arthritis.



ANTIRHEUMATIC EFFECT of aspirin is evident in this photograph of hind feet of a rat that had received daily doses of aspirin starting one day before the injection of tubercle bacilli. Photographs were made by B. B. Newbould of Imperial Chemical Industries.

atom of the carboxyl group has been replaced by a sodium atom and the hydroxyl group by an acetyl group. After 22 minutes the chemist tested a sample of his own urine for the presence of acetylsalicylate and free salicylate. The latter was present, but the urine gave no reaction for the acetyl compound. Over the next 12 hours the urine gave the same reactions, and Dreser concluded that acetylsalicylates readily decomposed in the body, liberating the therapeutically active salicylate. Observing that acetylsalicylic acid had "a pleasant sharp taste" instead of the sweet, nauseating flavor of sodium salicylate, and that it "acted more gently on the walls of the stomach," Dreser recommended it as a pharmaceutical preparation.

The first physicians to describe the medicinal uses of aspirin were Kurt Witthauer and Julius Wohlgemut of Germany. Their 1899 papers did not suggest that aspirin, either as a solid or as a liquid, had therapeutic effects greater than those of earlier salicin derivatives. Instead they emphasized the pharmaceutical advantages cited by Dreser, such as acceptable taste and decreased irritation of the stomach lining.

Only a year later—following the production of aspirin tablets "so cheap that no obstacle stands in the way of their use" and a small explosion of papers on aspirin in the medical journals—Witthauer wrote a second paper in which he described the unexpected potency of aspirin as a relief for pain in such varied conditions as migraine, persistent headache and inoperable carcinoma. Patients and their physicians had discovered in aspirin an analgesic so effective that its success misled them into extravagant optimism.

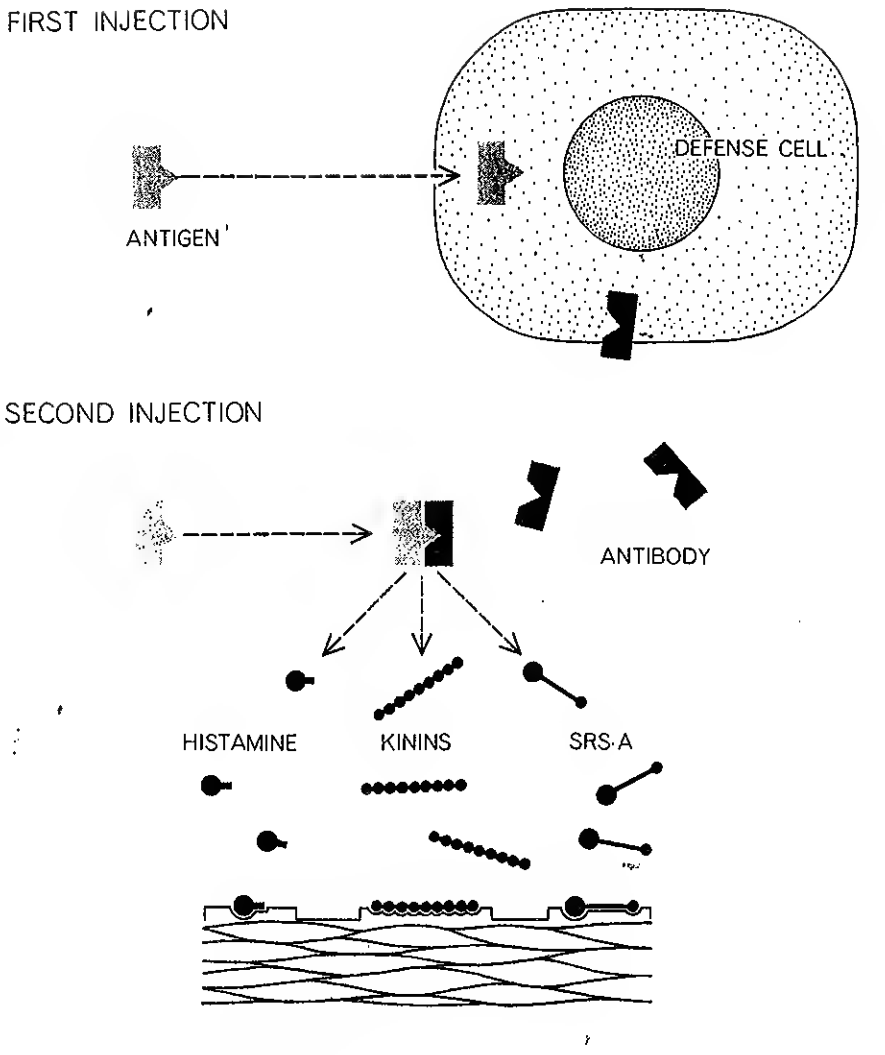
Witthauer himself warned that tablets "should not be swallowed whole but allowed to disintegrate first in a little sugar water flavored with 2 drops of lemon juice." Many ignored his advice and swallowed crude tablets of aspirin, which, disintegrating slowly and unevenly in the stomach, brought lumps of acetylsalicylic acid into contact with the stomach wall, with damaging results. Most modern aspirin tablets are designed to promote quick dissolution and so reduce the time in which an acidic lump can touch the stomach wall. Some tablets form the soluble calcium salt of acetylsalicylic acid as they dissolve in the stomach juices, whereas others yield a solution of the sodium salt in a glass of water prior to administration. Some capsules enclose the drug in a coat that

resists the acid of the stomach and dissolves in the alkaline juice of the small intestine. Although each of these is less likely to injure the stomach than the plain aspirin tablet, a real risk remains, as is indicated by the gastrointestinal bleeding that in some individuals can follow the taking of aspirin and by the fact that acetylsalicylic acid and its chemical relatives can produce stomach ulcers in rats, even when these drugs are injected under the skin rather than swallowed.

In some people aspirin induces an allergic hypersensitivity; thereafter a small dose has been known to provoke a fatal reaction. Because aspirin is incorporated in many medicaments, the occasional sufferer of the allergic reaction must be wary of this hazard. An interesting footnote to the "dangers" of aspirin is the listing in a chemical index of four of its helpful effects ("analgesic, antipyretic, antirheumatic, uricosuric") and 31 hazardous effects.

It has always been easier to catalogue the wide application of aspirin to man's commonest ills than to explain its mode of action. As an analgesic it relieves pain rapidly, inexpensively and effectively. Unlike morphine, it does not give rise to physiological dependence and may therefore be used freely for everyday aches, pains and malaises: headache, dysmenorrhea, hangover and so on. As an antipyretic, aspirin brings fever down by increasing sweating and the flow of blood through the skin. As an antirheumatic, it reduces the inflammation and pain in the joints and permits increased mobility. As a treatment for gout, it has both these effects and induces the excretion of uric acid, thus lessening the deposits of urate that form in the joints. There is no doubt about the usefulness of the drug. If the precise nature of its biochemical action remains a mystery, it is because so little is known about the biochemistry of the defensive responses, such as pain, fever and inflammation, evoked in the body by disease.

Early clinical studies indicated that the dose of aspirin for effective treatment of rheumatic fever, rheumatoid arthritis or gout virtually equaled that of sodium salicylate. This supported Dreser's view that aspirin acts by liberating salicylate within the body. When it came to the relief of pain, however, the situation soon appeared to be different: smaller doses of aspirin sufficed for effective treatment. Some investigators began to wonder what role



A MODE OF ACTION FOR ASPIRIN is suggested at bottom of this generalized view of bronchospasm in guinea pigs. An injection of antigen (*top*) signals antibody production. After a second injection the antigens react with antibodies to form histamine, kinins and the substance designated SRS-A, all of which induce a constriction of the bronchioles. This bronchospasm can be stopped if animal is treated with antibistamine, shown at bottom to block the action of bistamine, and aspirin, which in this case antagonizes kinins and SRS·A.

the liberation of salicylate could play if aspirin itself was the more potent of the two substances.

The problem assumed clearer shape when in 1946 David Lester, Ciorgio Lolli and Leon A. Greenberg of Yale University reported the results of their examination of the substances present in the blood plasma of volunteers who had taken a single oral dose of aspirin. As much as a quarter of the total dose, with the acetyl group still attached to the compound, could be detected in the blood for one to two hours after ingestion. The period during which aspirin was present intact in the blood corresponded with the duration of its analgesic action; hence the Yale workers argued that aspirin had an analgesic action independent of the salicylate it might release on decomposing.

In order to bring these findings back into line with Dreser's view it was suggested that some special characteristics of the distribution of aspirin to the tissues enabled it to liberate salicylate at sites of action that this substance alone could not reach. Doubt has been cast on this explanation by the discovery of other situations in which the potency of aspirin greatly exceeds that of the salicylate. One of these, which will serve as an example, involves thurfyl nicotinate, a substance that is sometimes applied to the skin as a counterirritant in muscular pain, sciatica and neuralgia.

When a cream that contains thurfyl nicotinate is rubbed into the skin, it evokes reddening and wealing. This is probably a local expression of the generalized skin flush that follows the swallowing of a tablet of nicotinic acid. In 1952 J. R. Nassim and H. Banner reported that the usual skin reaction to thurfyl nicotinate was not observed in patients with rheumatoid arthritis. For some years this was taken to be a sign of the disease. In 1959 L. H. Truelove and J. J. R. Duthie of the Northern General Hospital in Edinburgh showed that the effect was caused not by arthritis but by the aspirin with which the patients were regularly treated. In normal volunteers a single 10-grain (650 milligram) dose of aspirin delayed the reddening and abolished the swelling after thurfyl nicotinate was rubbed into the skin.

At the Salicylate Symposium in London in 1962 S. S. Adams and R. Cobb of the Boots Pure Drug Company described how they had tested the ability of several antirheumatic drugs to modify the skin response to thurfyl nicotinate. They found aspirin to be surprisingly potent: a single dose of 3.5 grains (225 milligrams) by mouth was detectably effective, and a 10-grain dose inhibited the skin response for several days. Neither sodium salicylate nor phenylbutazone, both useful antirheumatic drugs, was active at the dosage tested; taking into account the fact that decomposition in the bloodstream will allow no more than a quarter of the aspirin to reach the skin as the acetyl compound, it can be estimated that acetylsalicylic acid is at least 12 times more potent than sodium salicylate against thurfyl nicotinate.

This experiment indicates that acetylsalicylate has a medicinal effect in its own right, without having to be broken down first to salicylate as Dreser supposed. It does not show that the actions of the two drugs are qualitatively different, since a still larger dose of sodium salicylate might have shown activity.

A powerful stimulus to the study of how aspirin exerts its effects has been the desire of pharmaceutical manufacturers to find new drugs that have the therapeutic virtues of aspirin without its disadvantages. Here laboratory models of disease, or the body's various responses to disease, play a fundamental role. These models are set up in animals or in isolated living tissue. To be valid they must not only resemble the human disease and its symptoms but also react comparably to drugs.

Fever, rheumatoid arthritis and pain can be fairly well approximated in experimental animals. Of these, fever has proved the simplest to reproduce. Fevers in man usually arise during microbial infections, in which the invaders liberate minute quantities of substances called pyrogens. Pyrogens can be extracted from bacterial cultures, and they produce fevers when injected into laboratory animals. For example, the injection of half a microgram (half a millionth of a gram) of pyrogen extracted from cultures of *Bacillus proteus* will raise the rectal temperature of a rabbit by one to two degrees centigrade within an hour or two. This fever can be prevented by a relatively small dose of aspirin.

The main manifestation of rheumatoid arthritis is an inflammation of the joints, more simply "arthritis." An apparently close approximation of this condition can be induced in rats. In 1954 H. C. Stoerk, T. C. Bielinski and T. Budzilovich of the Merck Institute observed that rats developed a chronic arthritis when they were injected with emulsions of spleen cells suspended in an adjuvant consisting of dead tubercle bacilli in liquid paraffin, commonly used by pathologists to intensify the action of injected cells or bacteria. A few weeks after the injection swelling appeared in some of the joints of about half of the animals treated. Tails as well as limb joints were affected, and the swellings lasted, with occasional temporary lessening, for many months [*see illustrations on page 5*]. Under the microscope the swelling was seen to be caused by inflammation like that in human rheumatoid arthritis.

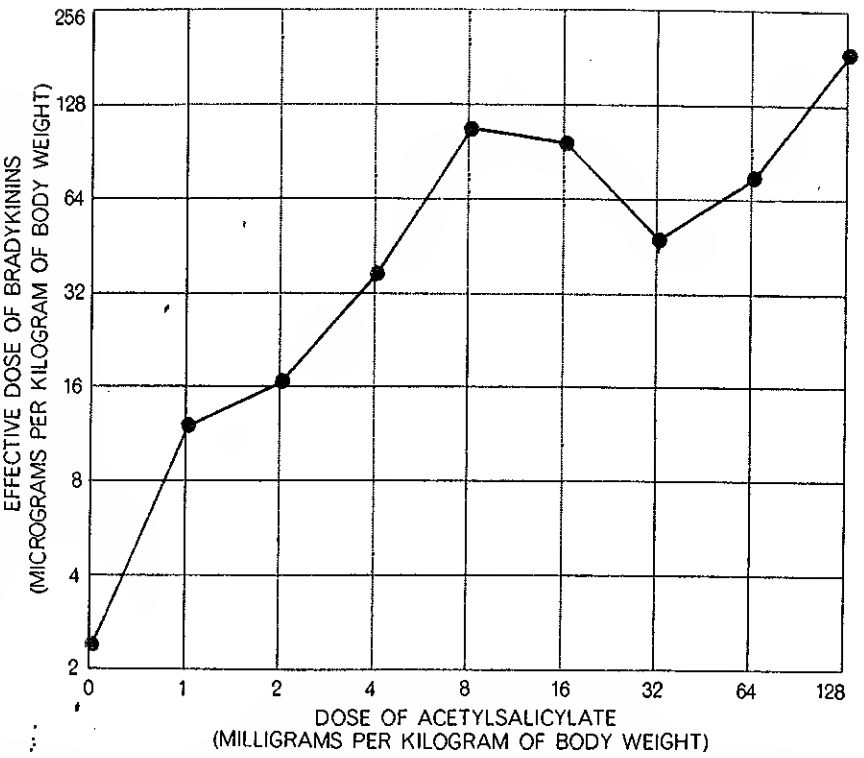
Stoerk and his colleagues attributed this chronic arthritis to the spleen cells injected into their rats. In 1956, however, Carl M. Pearson of the University of California School of Medicine in Los Angeles showed that the adjuvant alone, without any spleen cells suspended in it, would produce the same effect. Later Pearson and Fae D. Wood found that dead bacteria of other species of the genus *Mycobacterium*, to which the human tubercle bacillus belongs, were also effective, although bacteria of other genera were not. Even chemical extracts of tubercle bacilli can elicit this chronic arthritis in rats. The disease seems therefore to be an ultimate immunological response of the animal to a foreign chemical derived from a particular kind of bacterium. Conceivably rheumatoid arthritis arises from similar causes in man.

In the treatment of arthritis the hormones of the adrenal cortex and other steroid hormones have proved to be most effective in both human beings and rats. Recently B. B. Newbould of the Imperial Chemical Industries has found that acetylsalicylic acid, sodium salicylate, phenylbutazone, aminopyrine and flufenamic acid, the most effective types of nonsteroidal agents in the treatment of human rheumatoid arthritis, show corresponding potencies when administered to rats. Newbould's research indicates that among drugs known to be effective against the human disease only the quinoline antimalarials are ineffective against the rat arthritis. His experiments thus affirm the similarity between the laboratory model of arthritis and the human disease and demonstrate the powerful anti-inflammatory action of aspirin and related drugs.

It has proved difficult to develop equally persuasive laboratory models of pain and the objective measurement

of the analgesic effect that motivates most use of aspirin. In a few animal experiments aspirin could be shown to raise the intensity of noxious stimulation needed to elicit a protective response, but the magnitude of the effect was small and the dose required correspondingly large. In 1956, however, Christine Vander Welde and Sol Margolin of the Schering Corporation described a model pain situation in which the injection of a noxious chemical solution into the abdominal cavity of rats or mice produces a characteristic constriction of the abdominal wall followed by extension of the hind legs. The response, which has been termed "stretching" or "writhing," was usually repeated several times after the injection. The inference that this response signifies pain is supported by the actions of drugs. Local anesthetics suppress the response when they are injected at the site, and analgesics suppress it when they are administered by any route. In a mouse a dose of about 20 micrograms of morphine effectively reduces writhing, and a dose of about one milligram of aspirin is correspondingly active. For this model situation, then, it can be said that aspirin has about a fiftieth of the analgesic effect of morphine. This corresponds with human experience; on the subjective testimony of patients it is said that 300 to 1,000 milligrams of aspirin relieves pain about as well as 10 to 30 of morphine.

The suggestion has been made that aspirin acts in mice and men by antagonizing natural pain substances such as the peptides called kinins, which are released locally in the blood and tissues at the site of injury [see "Kinins," by H. O. J. Collier; SCIENTIFIC AMERICAN, August, 1962]. Robert K. S. Lim and his co-workers at the Miles Laboratories have performed ingenious experiments in dogs showing that aspirin blocks the action of one of these kinins (bradykinin) and suppresses its excitation of the nerve endings in the viscera that promote pain sensation. Bradykinin also evokes the writhing response when it is injected into the abdominal cavity of mice, and this too is blocked by aspirin. It has not been established that aspirin blocks the pain evoked by bradykinin more effectively than it blocks pain signaled by other substances; nor has aspirin been found to block all the types of pain caused by bradykinin. For example, bradykinin injected into the skin of guinea pigs elicits scratching and licking at the site of the injection; aspirin does not prevent these responses, although morphine does.



ANTAGONISM of bradykinin inducing bronchospasm in the guinea pig is graphed by plotting the dosage of acetylsalicylate injected (*horizontal axis*) against the quantity of bradykinin needed to cause constriction of the bronchioles (*vertical axis*). Experiment was performed by the author and Patricia G. Shorley at Parke, Davis & Company in England.

In the most illustrative experiments exploring aspirin's mode of action on the molecular level, the disease duplicated in the laboratory was bronchial asthma. Significantly, a disease can be described in terms of various elements, such as the invading agent (for example the influenza virus), the body's response (rheumatic fever) or the ultimate damage inflicted (infantile paralysis). Human bronchial asthma, which fits the second descriptive category, is the reaction of the bronchioles to the inhalation of a small amount of a specific antigen, usually a foreign protein present in a pollen or in the dander of an animal. Like fever, pain or arthritic inflammation, then, asthma represents the type of unwarranted or excessive bodily response to an invading agent that aspirin seems able to mitigate.

A crude example of asthma in the guinea pig has been observed for half a century. If a single dose of foreign protein such as egg white or horse serum is injected, it does little harm to the guinea pig. But a second dose a few weeks later causes an intense reaction in which the muscular walls of the bronchioles contract violently. The resulting constriction of the bronchioles, or bronchospasm, usually hinders breathing so drastically as to be fatal. This is one of the more familiar and extreme forms of the distorted immunological response known as anaphylactic shock. In response to the first injection of antigen, defense cells produce an antibody tailored to fit the substance [see "The Mechanism of Immunity," by Sir Macfarlane Burnet; SCIENTIFIC AMERICAN, January, 1961]. When the antigen is injected a second time, it reacts with the antibody to produce anaphylactic shock [*see illustration on page 7*].

Human bronchial asthma is a much milder reaction of the bronchioles to inhalation of a dust containing a small amount of antigen to which the sufferer has become sensitized. A precise equivalent of human asthma in the guinea pig was set up in 1952 by Herbert Herxheimer, then at the University College Hospital Medical School in London, who caused animals previously sensitized to egg albumen to inhale a solution of it in a fine mist.

As long ago as 1910, at the Wellcome Physiological Research Laboratories in England, Sir Henry Dale and Sir Patrick P. Laidlaw had observed that the injection of histamine, a substance released by injured tissues, produces a bronchospasm like that of anaphylactic shock. Histamine had not long been syn-

thesized at that time and was still known under its chemical name of beta-imidazolylethylamine. After comparing many responses of various animals to histamine and to anaphylactic shock, Dale and Laidlaw wrote: "We content ourselves with recording, as a point of interest and possible significance, the fact that the immediate symptoms with which an animal responds to an injection of a normally inert protein, to which it has been sensitized, are to a large extent these of poisoning by beta-imidazolylethylamine."

This comment had a powerful influence on later investigations. In 1932 several teams of workers in different parts of the world showed that histamine is released during anaphylactic shock in the guinea pig. Then in 1937 Daniel Bovet and A.-M. Staub, working at the Pasteur Institute in Paris, described the first antihistamine drug, 929F. This drug not only protected guinea pigs against constriction of the bronchioles caused by inhaling histamine solution in a fine mist but also protected them to some extent against anaphylactic shock. Many other antihistamines followed 929F; all of them lessened anaphylactic bronchospasm but none abolished it altogether. This confirmed that the histamine released in anaphylactic shock played a part in constricting the bronchioles, but it also implied that some other factor was involved.

A search for other substances that are released during anaphylactic shock and might play a part in constricting the bronchioles in the guinea pig has so far implicated two. In 1940 C. H. Kellaway and E. R. Trethewic found a substance that has not yet been purified and chemically identified and is known by the awkward name of Slow Reacting Substance in Anaphylaxis, or SRS-A. The other substance is the family group of kinins, as W. E. Brocklehurst and S. C. Lahiri of the University of Edinburgh demonstrated in 1961.

Previously John A. Holgate, Mel Schachter, Patricia C. Shorley and I, working at the laboratories of Parke, Davis & Company in England and at University College London, had shown that intravenous injection of kinin into normal guinea pigs causes constriction of the bronchioles, and in 1962 P. A. Berry, Holgate and I showed that SRS-A acts in a similar way. We also found that the bronchospasm induced by either kinins or SRS-A can be completely prevented by the administration of a small dose of aspirin a few minutes before the injection.

Although aspirin has no such effect on the action of histamine, it appears to act as a specific chemical antagonist of kinins and SRS-A, just as antihistamines antagonize histamine. If the three substances are jointly responsible for the bronchospasm, one might expect that treatment with both aspirin and antihistamine would prevent it and that either drug alone would be partly effective. Within the past year Alexander R. Hammond, Barbara Whiteley and I have found strong evidence in support of this prediction. In this particular model of asthma, at least, it appears that aspirin acts as a pharmacological antagonist of kinins and SRS-A. This effect is probably achieved by the molecules of aspirin blocking a reaction between the molecules of kinin, SRS-A and the bronchial muscle they stimulate.

The question of how closely the guinea pig model of asthma resembles the human counterpart has occupied more than a generation of research workers. In 1951 H. O. Schild, Denis F. Hawkins, Jack L. Mongar and Herxheimer, working at University College London, showed that a piece of human bronchial muscle, removed from an asthma sufferer during a surgical operation and suspended in a suitable saline medium, released histamine when it was exposed to the pollen to which the patient was hypersensitive. In 1955 Brocklehurst, then working at the National Institute for Medical Research in London, found that contact with the appropriate antigen also released SRS-A from isolated fragments of a human asthmatic lung. Recently Herxheimer and E. Stresemann, working at the Free University of West Berlin, have demonstrated that when volunteers susceptible to asthma inhale a solution of either bradykinin or SRS-A in a fine mist, an asthmatic attack follows. From clinical experience it is known that aspirin and antihistamines, when taken separately, ameliorate asthma slightly in human patients. But it is not yet established that the two drugs, taken together, would have a stronger effect, or that aspirin acts as a pharmacological antagonist of kinins or SRS-A in the human lung.

Whether aspirin, in its vast consumption, is taken as an antipyretic, analgesic or antirheumatic, its general function seems to be the moderation of the defensive reactions to various forms of disease. It would appear that the human body has an unwieldy defense establishment that aspirin fortunately can help to control.